Towards faster studies of neonatal encephalopathy

Published Online
November 14, 2018
http://dx.doi.org/10.1016/S1474-4422(18)30370-3

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Cooling was first suggested for the treatment of brain injuries several millennia ago.[1] There is now compelling evidence that therapeutic hypothermia for moderate to severe neonatal encephalopathy significantly improves survival and reduces disability in infancy.[2] However, a meta-analysis suggested an absolute reduction in risk of approximately 15%, from 61% to 46%,[2] meaning that nearly half of infants die or survive with disability despite treatment. A large trial[3] has shown that existing protocols for therapeutic hypothermia are very close to optimal. Given that a range of interventions show encouraging neuroprotection in animal studies,[4] progress is most likely to come from incremental trials of these candidate therapies. Neonatal trials largely use neurodevelopmental follow-up to 18–24 months of age as a measure of outcome. This is appropriate, but substantially prolongs the time needed to complete each study. Biomarkers of outcome could substantially speed up each trial.

The best existing biomarker, conventional MRI, measures a biological change that is directly linked to both the injury process and patient outcome. Changes visible in the scans are associated with neurodevelopmental outcomes[5] but MRI does not perform well enough as the primary outcome of a trial because it can overpredict adverse neurodevelopmental outcome and, conversely, miss some cases of adverse outcome. Magnetic resonance (MR) spectroscopy is also highly predictive in single-centre studies but has not been widely taken up in clinical practice because of differences in calibration between the various models of MR scanners. In *The Lancet Neurology*, Peter J Lally and colleagues report results of the magnetic resonance biomarkers in neonatal encephalopathy (MARBLE) study,[6] a prospective multicentre cohort study of 223 infants with neonatal encephalopathy who were all treated with hypothermia and then had MR imaging and proton spectroscopy within 14 days after birth; 190 (85%) had neurodevelopmental follow-up at a median age of 23 months. Spectroscopy was highly predictive of neurodevelopmental outcomes, with an area under the curve (AUC) for the peak-area ratio of lactate to N-acetylaspartate (NAA)—found in large amounts in neurons and oligodendrocytes—of 0·94 (95% CI 0·89–0·97). Remarkably, in the 82 infants for whom thalamic concentrations of NAA were available, the AUC was 0·99 (0·94–1·00), with a far higher prognostic accuracy than conventional MRI (98% [95% CI 91–100] *vs* 87% [81–91] for injury to the posterior limb of internal capsule assessed by MRI, which had the highest accuracy of all MRI assessments).

The reason for this tight association is probably that the thalamus is highly susceptible to injury and, in turn, associated with disabilities that can be assessed at 2 years of age. A potential limitation would be that, in animal studies, very mild hypoxic-ischaemic injury has been shown to cause isolated hippocampal damage,[7] which would be associated with academic problems in mid-childhood, without neuromotor disability. Furthermore, some of the infants classified as having mild neonatal encephalopathy might have had moderate but more slowly evolving encephalopathy,[8] as suggested by the wide overlap in outcomes between the mild and moderate groups.[6]

Intriguingly, the overall rate of adverse outcome was extremely low, with just 31 (16%) infants showing abnormal neurodevelopment at 2 years. It is not completely clear why the event rate was so much lower than in treated infants with moderate to severe neonatal encephalopathy in either the original trials of therapeutic hypothermia (about 46%)[2] or a recent large trial (29%).[3] In part, the low rate of adverse outcome might reflect the translation of therapeutic hypothermia to routine care, and changes such as wide use of passive cooling after resuscitation. Additionally, given that the rate of adverse outcome after severe neonatal encephalopathy (13 [57%] of 23 infants)[6] was essentially the same as in the randomised controlled TOBY trial[2] (109 [56%] of 193 infants), the low overall rate in the MARBLE study probably reflects inclusion of infants with milder neonatal encephalopathy in the first 6 h of life who would have been excluded from previous studies.

The recent PRIME study[9] suggests that infants with mild neonatal encephalopathy in the first 6 h of life who are not treated with hypothermia have a 16% risk of disability[9] compared with 3% in infants treated with therapeutic hypothermia in the MARBLE study.[6] Infants with mild neonatal encephalopathy were excluded from the original randomised controlled trials of therapeutic hypothermia.[2] Thus, this encouraging apparent benefit after treatment in the MARBLE study supports that it is

urgent to undertake pragmatic trials of treatment for mild neonatal encephalopathy. Early MR spectroscopy would strengthen such trials.

In conclusion, this demonstration of the extremely high prognostic accuracy for MR spectroscopic measurements of NAA concentration will enable much faster incremental studies of neonatal encephalopathy because it offers robust measurement of outcome within weeks. Moreover, the reference data from the MARBLE study will be made available, allowing MR sequences, and thus individual patient scans, to be done more rapidly within large pragmatic studies. Clinicians in this field can look forward to an era of clinical research in which it is no longer necessary to delay gratification for years!

Alistair J Gunn, Malcolm Battin
Department of Physiology, University of Auckland, Auckland 1023, New Zealand (AJG) and Newborn Services, Auckland City Hospital, Auckland, New Zealand (MB)
ajgunn@auckland.ac.nz

We are supported by the Health Research Council of New Zealand and the Neurological foundation of New Zealand. We declare no competing interests.

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Patients with large brain infarcts might also benefit from thrombectomy

Published Online November 6, 2018 http://dx.doi.org/10.1016/S1474-4422(18)30357-0

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The biological premise of acute stroke therapy rests on time (specifically, the duration of focal cerebral ischaemia) and the presence in these patients of an ischaemic penumbra, an intermediate zone of oligaemia between normal cerebral blood flow and complete ischaemia that surrounds a core region of irreversibly injured tissue. The penumbra, distal to an arterial occlusion and variably supported by collateral blood flow, is potentially salvageable brain tissue that will, in the absence of timely reperfusion, progress at variable rates to become part of the core infarct. Reperfusion of an ischaemic core that has no surrounding penumbra would, by definition, be futile.[1]

The clinical trials that have shown efficacy of endovascular thrombectomy initiated within 6 h of onset of ischaemic symptoms required prerandomisation evidence of acute occlusion of the internal carotid or middle cerebral artery, implying the presence of a penumbra, but they did not require imaging evidence of the ischaemic core or penumbra. These trials found that thrombolysis with endovascular thrombectomy was more effective than standard medical management when they achieved earlier recanalisation and reperfusion.[2,3]

The results of a meta-analysis of these clinical trials by Bruce Campbell and colleagues[4] in *The Lancet Neurology* offer important insights into the question of whether the benefit of recanalisation relates to the volumes of ischaemic core or penumbra. They pooled individual-level data for 1764 patients from the seven randomised controlled trials. Within this pooled sample, 900 patients had prerandomisation CT perfusion (n=591) or MRI diffusion-weighted (n=309) images that were analysed to estimate ischaemic core and penumbral volumes. Because only 33 (11%) of the patients in whom MRI was obtained had perfusion MRI, the MRI patients were only used to estimate ischaemic core volume, defined as the region with an apparent diffusion coefficient threshold of less than 620 m^2/s. From CT perfusion images, the ischaemic core was defined as cerebral blood flow less than 30% of normal brain, critically hypoperfused tissue